

The mapping between Chinese medicine and signaling molecules

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Abstract

Knowledge of signal transduction pathways and their corresponding signaling molecules is critical in evaluating potential therapeutic targets. Traditional Chinese Medicine (TCM) used Yang and Yin to describe the physiological processes in human body, but its scientific basis is unknown. According to “Yellow Emperor’s Inner Canon” (YEIC)—the fundamental doctrinal source for TCM—there are five elements of Yang-Yin, each pertaining to particular physiological functions. Their interaction and relationship determine the physiological conditions of human being. In this work, iterative selection method was used to correlate Yang-Yin-Qi with signal molecules. It is revealed that the signal transduction pathways are identical to the dialectical relationships of Yang-Yin-Qi(s). With the direct mapping between Yang-Yin-Qi(s) and signaling molecules, the signal transduction pathways are consistent with TCM therapeutic strategies too. In addition, it is demonstrated that the Chinese herbal medicine regulates signal transductions. With the correlation between Yang—Yin(s) and signal transduction pathways, it is evident that the modern medicine and TCM identified the same pathogenesis of diseases, such as hematuria, constipation, hemorrhoidal disease, nocturnal enuresis, frequent urination, gall stone, acute cholecystitis and hypertension, etc; with highly similar treatment strategy, albeit using different terminologies.

Key words: Signaling molecules, traditional Chinese medicine, pathways, Yang and Yin, therapeutic strategy.

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Glossary

AKR	aldo-keto reductase, Liver Yin in TCM
Ang	Angiotensin, Heart Yin in TCM
ANP	atrial natriuretic peptide, Spleen Yang in TCM
EPO	Erythropoietin, Liver Yang in TCM
FGF7	fibroblast growth factor-7, Lung Yang in TCM
Five Phases	TCM term, includes heart phase, spleen phase, lung phase, kidney phase, liver phase
GSH	Glutathione, Liver Qi in TCM
Heart phase	TCM term, includes heart organ, Heart Yang, Heart Yin, and Heart Qi
HGF	hepatocyte growth factor, Liver Yang in TCM
HIF	hypoxia inducible factor, Lung Qi in TCM
IGF	insulin-like growth factor, Heart Yang in TCM
Kidney phase	TCM term, includes kidney organ, Kidney Yang, Kidney Yin, and Kidney Qi
Liver phase	TCM term, includes liver organ, Liver Yang, Liver Yin, and Liver Qi
Lung phase	TCM term, includes lung organ, Lung Yang, Lung Yin, and Lung Qi
Mg	Magnesium, Heart Qi in TCM
NO	nitric oxide, Kidney Qi in TCM
PTHrP	parathyroid hormone-related protein, Kidney Yin in TCM
Qi	substance in TCM, has function of activation and regulation
SOD	superoxide dismutase, Liver Yin in TCM
Spleen phase	TCM term, includes spleen organ, Spleen Yang, Spleen Yin, and Spleen Qi
TCM	traditional Chinese medicine
VEGF	vascular endothelial growth factor, Lung Yang in TCM
Yang	Key substance in TCM, has function of warming/developing/proliferation
YE-81	Yellow Emperor's Classic on 81 Medical Problems
YEIC	Yellow Emperor's Inner Canon
Yin	Key substance in TCM, has function of cooling and astringent

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1. Introduction

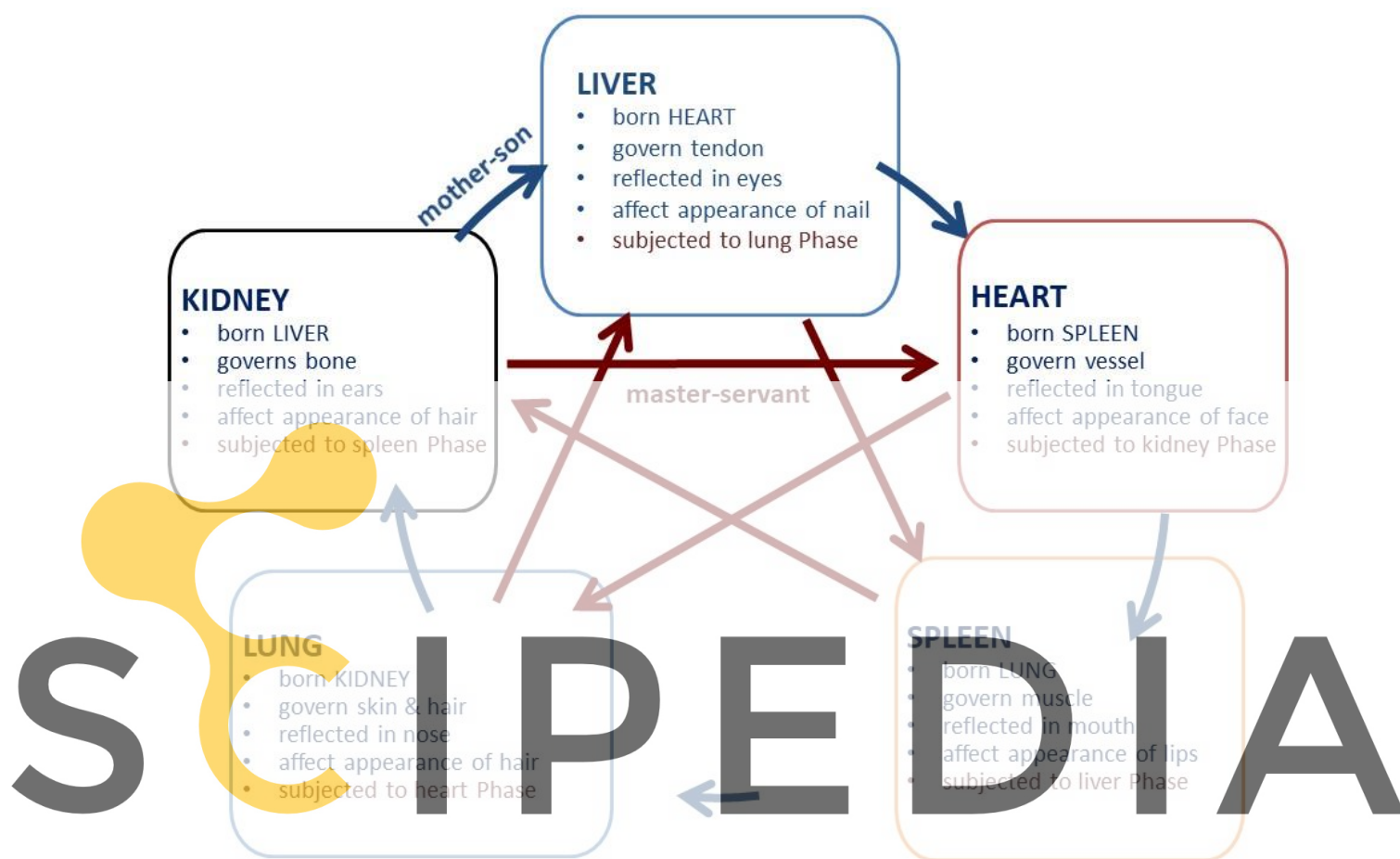
The transduction pathways of signaling molecules are important to understanding how signaling molecules regulate physiological function and also in predicting the pathological development which is important to therapeutic strategy. However, despite the documented importance of signaling molecules to human life, we still lack thorough knowledge of transduction pathways of signaling molecules.

Traditional Chinese medicine (TCM) has been effective for thousands of years in China. Ancient TCM physicians believed that there existed key substances to regulate the physiological processes and named them as Yang and Yin, where Yang has warming/developing function and Yin has cooling/astringent function. Yang and Yin are contrary but interdependent in human body. According to the physiological functions of these key substances, ancient TCM physicians categorized these Yang and Yin into heart phase, spleen phase, lung phase, kidney phase and liver phase, i.e., the Five Phases. Besides Yang and Yin, TCM physicians also found there existed another substance in each organ phase whose function is actuation/regulation, and they named it as Qi. Thus, each organ phase includes the organ itself, and the organ's Yang, Yin and Qi. According to "Yellow Emperor's Inner Canon" (YEIC) [1], the fundamental doctrinal source for TCM, each organ phase has particular physiological functions, and the Five Phases regulate each other and follow the "mother-son" and "master-servant" relationships (Figure 1). Therefore, TCM physicians developed diagnosis theories and therapeutic strategies based on these dialectical interrelationships.

However, there is an obstacle to developing a general frame work linking TCM theory and modern physiology, i.e., one cannot scientifically identify Yang, Yin and Qi of each organ. Due to the tremendous studies in recent years on signaling molecules, we have an unprecedented opportunity to explore the link between TCM theory and life science. To establish the mapping between Yang-Yin-Qi and signaling molecules, one have to meet four criteria:

- (i) The Yang-Yin-Qi(s) have particular physiological functions in TCM, and the corresponding signaling molecule should show the same ones.
- (ii) TCM demonstrated the interrelationships of Five Phases, and the transduction pathways of these signaling molecules should follow the same relationships.
- (iii) The Chinese herbal medicine has its particular function to regulate Yang-Yin-Qi, and the herbal medicine could regulate the corresponding signaling molecules as well.
- (iv) There have been eight famous TCM treatment principles, and these eight TCM principles should be consistent with the transduction pathways of the corresponding signaling molecules.

Here we use the iterative selection method to establish the direct mapping between these Yang-Yin and signaling molecules through two steps. First, we identified the signaling molecules for Yang or Yin or Qi of each organ phase based on the above criteria (i) and (ii); second, we validated our mapping according to the above criteria (iii) and (iv). With the mapping, we showed that the modern medicine and TCM could identify the same pathogenesis of diseases, such as hematuria, constipation, hemorrhoidal disease, nocturnal enuresis, frequent urination, gall stone, acute cholecystitis, hypertension and diabetes. The modern medicine and TCM describe the same physiological processes using different terminology.



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Figure 1. The functions and interrelationships of the Five Phases in TCM. The Heart phase should be generated in liver, govern blood vessel, and be enlightened in tongue; and its prosperity is reflected by face. The Spleen phase should be generated in heart, govern muscle, and be enlightened in mouth; and its prosperity is reflected by lips. The Lung phase should be secreted in spleen, govern skin and hair, and be enlightened in nose; and its prosperity is reflected in body hair. The Kidney phase should be generated in lung, govern bone, be enlightened in ears, and affect the appearance of “paw” (finger, toe, nail). Furthermore, Heart phase is connected with small intestine, Spleen phase is connected with stomach, Lung phase is connected with large intestine, Kidney phase is connected with bladder, and Liver phase is connected with gallbladder. The arrow along outer circle denotes the “mother-son” relationship, and the arrow along the diagonal direction indicates the “master-servant” relationship.

2. Iterative Selection Method and mapping results

Using the functions of Heart phase, Spleen phase, Lung phase, Kidney phase and Liver phase in TCM as constraint conditions, we apply the following Iterative Selection method to identify the signaling molecules. Suppose the signaling molecules form the following set,

$X = \{x: \text{signaling molecules}\}$, and Heart phase, Spleen phase, Lung phase, Kidney phase and Liver phase are A, B, C, D, E, respectively.

Step 1: identify the signaling molecules in each organ

There are four constraint conditions in each organ as shown in Figure 1.

$\varphi_A(u_1, u_2, u_3, u_4)$ denotes the four conditions in Heart phase, where

u_1 : the molecule should have significant effect on heart,

u_2 : the molecule governs blood vessel,

u_3 : the molecule is enlightened in tongue,

u_4 : the molecule affects the appearance of face.

$\varphi_B(u_1, u_2, u_3, u_4)$ denotes the four conditions in Spleen phase, where

u_1 : the molecule should have significant effect on spleen,

u_2 : the molecule governs muscle,

u_3 : the molecule is enlightened in mouth,

u_4 : the molecule affects the appearance of lips.

$\varphi_C(u_1, u_2, u_3, u_4)$ denotes the four conditions in Lung phase, where

u_1 : the molecule should have significant effect on lung,

u_2 : the molecule governs hair and skin,

u_3 : the molecule is enlightened in nose,

u_4 : the molecule affects the appearance of body hairs.

$\varphi_D(u_1, u_2, u_3, u_4)$ denotes the four conditions in Kidney phase, where

u_1 : the molecule should have significant effect on kidney,

u_2 : the molecule governs bone,

u_3 : the molecule is enlightened in ears,

u_4 : the molecule affects the appearance of hairs.

$\varphi_E(u_1, u_2, u_3, u_4)$ denotes the four conditions in Liver phase, where

u_1 : the molecule should have significant effect on liver,

u_2 : the molecule governs tendon,

u_3 : the molecule is enlightened in eyes,

u_4 : the molecule affects the appearance of paws.

Then, compare X with φ , and obtain the class Y ,

$Y = \{x: \varphi_i(u_1, u_2, u_3, u_4)\}$, for Heart phase, Spleen phase, Lung phase, Kidney phase and Liver phase, respectively.

Step 2: identify Yang, Yin and Qi for each organ

In TCM, Yang has developing/warming effect, Yin has astringent/cooling effect, and Qi has the function of activation/regulation. These constraint conditions are set as ϕ_1 , ϕ_2 , and ϕ_3 . Then, compare class Y with ϕ_1 , ϕ_2 , and ϕ_3 respectively, and obtain either Yang, or Yin, or Qi for each organ phase:

A1 = {y: ϕ_1 }, A2 = {y: ϕ_2 }, and A3 = {y: ϕ_3 };
 B1 = {y: ϕ_1 }, B2 = {y: ϕ_2 }, and B3 = {y: ϕ_3 };
 C1 = {y: ϕ_1 }, C2 = {y: ϕ_2 }, and C3 = {y: ϕ_3 };
 D1 = {y: ϕ_1 }, D2 = {y: ϕ_2 }, and D3 = {y: ϕ_3 };
 E1 = {y: ϕ_1 }, E2 = {y: ϕ_2 }, and E3 = {y: ϕ_3 }.

Step 3: refine the selection according to “mother-son relationship” in Figure 1

Since Yang has developing effect, according to the “mother-son” relationship, the organ Yang should be secreted from the “mother” organ, e.g., Kidney Yang should be secreted from lung. We use this condition to refine the A, B, C, D, E in Step 2.

Step 4: refine the selection by comparing pathways

We compare the pathways of signaling molecules with the interrelationships of the Five Phases in Figure 1 to further refine the selection in Step 3.

Step 5: validate the selection based on Chinese herbal medicine

There are some clinical and experimental data to show that some TCM herbal medicine would regulate the signaling molecules, and we use these available data to validate the results in Step 4.

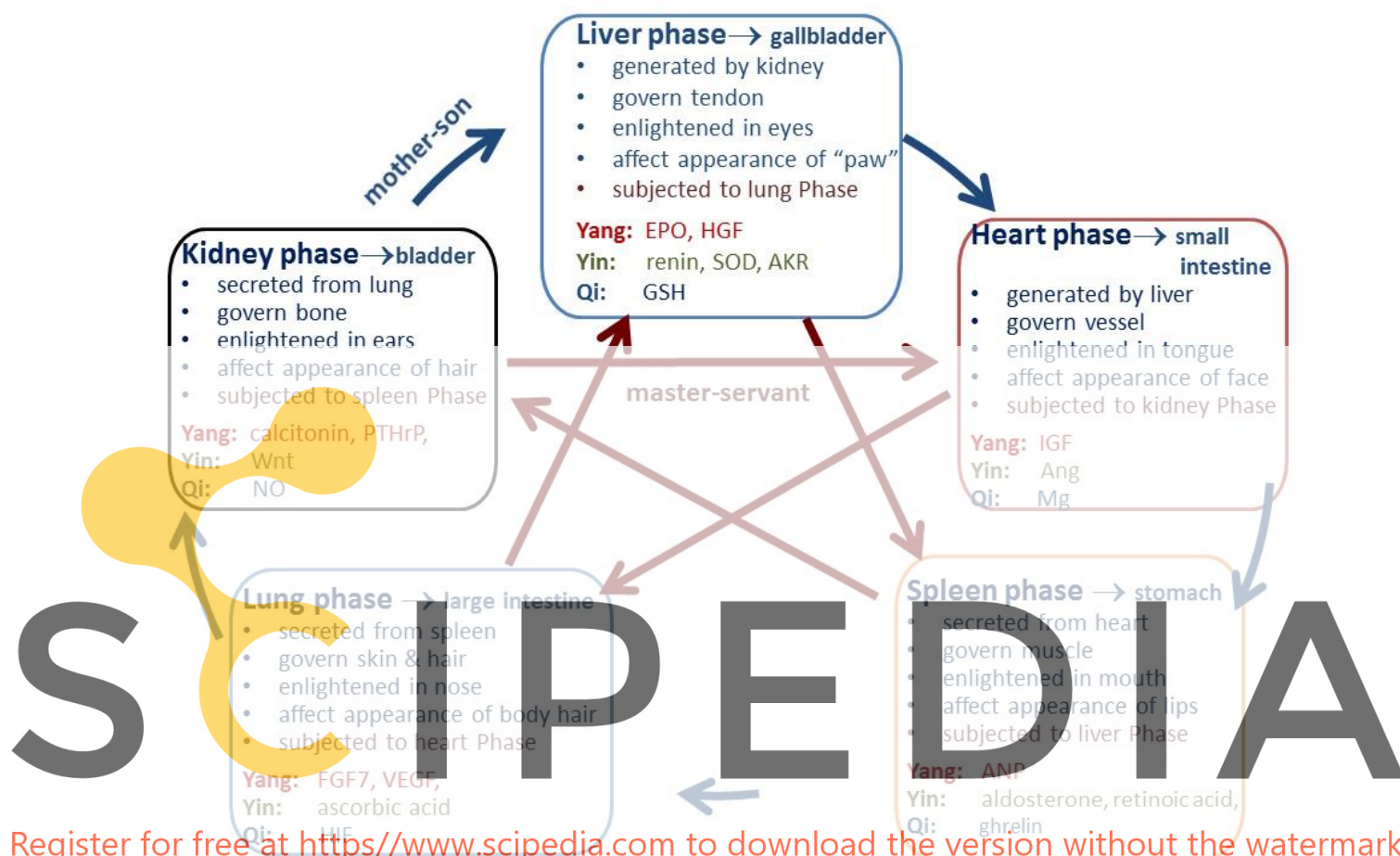
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The mapping between Yang-Yin-Qi of Five Phases and signaling molecules are tabulated in Table 1 and shown in Figure 2.

Table 1 Corresponding signaling molecules of each organ phase

	Yang	Yin	Qi
Heart phase	IGF	Ang	Mg
Spleen phase	ANP	aldosterone, retinoic acid	ghrelin
Lung phase	FGF7, VEGF	ascorbic acid	HIF
Kidney phase	calcitonin, PTHrP	Wnt	NO
Liver phase	EPO, HGF	renin, SOD, AKR	GSH



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Figure 2. The mapping between Yang-Yin-Qi of Five Phases in TCM and signaling molecules

3. Identifying the signaling molecules for Yang, Yin and Qi in each organ phase of TCM

According to the “Yellow Emperor’s Inner Canon” (YEIC) [1], the fundamental doctrinal source for TCM, the Heart phase should be generated in liver organ, govern blood vessel, and be enlightened in tongue; and its prosperity is reflected by face. The Spleen phase should be generated in heart organ, govern muscle, and be enlightened in mouth; and its prosperity is reflected by lips. The Lung phase should be secreted in spleen organ, govern skin and hair, and be enlightened in nose; and its prosperity is reflected in body hair. The Kidney phase should be generated in lung organ, govern bone, be enlightened in ears, and affect the appearance of hair. The Liver phase should be generated in kidney organ, govern tendon, be enlightened in eyes, and affect the appearance of “paw” (finger, toe, nail). Furthermore, Heart phase is connected with

small intestine, Spleen phase is connected with stomach, Lung phase is connected with large intestine, Kidney phase is connected with bladder, and Liver phase is connected with gallbladder.

3.1 Key substances of Heart phase are IGF, Ang and Mg

According to YEIC [1], the Heart phase should exert significant effect on heart organ, be generated in liver, govern blood vessel, and be enlightened in tongue. Moreover, the prosperity of Heart phase is reflected by face.

In physiological reality, IGF is secreted by liver and is important to heart function. IGF-1 signaling regulates metabolism, contractility, senescence, autophagy, hypertrophy, and apoptosis in the heart; it activates canonical and noncanonical signaling pathways in the heart; deficiency in IGF-1 may drive cardiovascular disease, and local IGF-1 therapy can prevent heart injuries in experimental models [2]. IGF system exerts multiple physiologic effects on the vasculature, and plays a role in multiple vascular pathologies, including hypertension, diabetic vascular disease, atherosclerosis, angiogenesis, and restenosis [3]. Chronic treatment with IGF-1 significantly improves the vasoreactivity [4]. IGF is also enlightened in tongue, its level affects the tongue size, with increasing IGF level, tongue weights significantly increase with histopathological changes present; when IGF level is back to normal, tongue size returns to control levels [5]. Moreover, IGF level is reflected in skin, and high levels of IGF associate with reduced skin wrinkling [6]. As IGF-1 has warming effect [7], we identify IGF as Heart Yang.

Ang is secreted by liver; Ang II regulates cardiac and blood vessel contractility, and is involved in cardiac growth, remodeling, and apoptosis [8]. Angiotensin-converting enzyme inhibitor induces tongue angioedema, indicating an important role of Ang in tongue [9]. Moreover, the complete renin-angiotensin system is present in human skin and plays a role in normal cutaneous homeostasis [10]. As Ang II induces hypothermia [11], we identify Ang as Heart Yin.

Mg is important to normal heart rhythm and is a cofactor in more than 300 enzyme systems that regulate diverse biochemical reactions in the body, including blood pressure regulation and blood glucose control [12]. Mg relaxes blood vessel [13]; and it is also enlightened in tongue, as patients with burning mouth syndrome at the anterior tongue exhibit Mg deficiency as manifested by lower than normal Mg levels in saliva and erythrocytes [14]. Moreover, Mg affects the appearance of skin, it was found that magnesium-rich Dead Sea salt solution enhances skin hydration, improves skin barrier function, and reduces inflammation in atopic dry skin [15]. Due to its strong regulation and actuation effect, we identify Mg as Heart Qi.

TCM considers that Yang and Yin regulate each other and Figure 3 shows the interrelationships of IGF, Ang and Mg. It was found that Ang II infusion in rat decreases levels of circulating and skeletal muscle IGF-1 [16], Ang II stimulates cardiac IGF-1 [17] and transcription of IGF-1 receptor in vascular smooth muscle cells [18], and IGF-1 reduces Ang II [19]. Moreover, the exposure of the platelets to Ang II significantly decreases intracellular Mg concentrations [20], and Mg levels are strongly associated with IGF-1 [21].

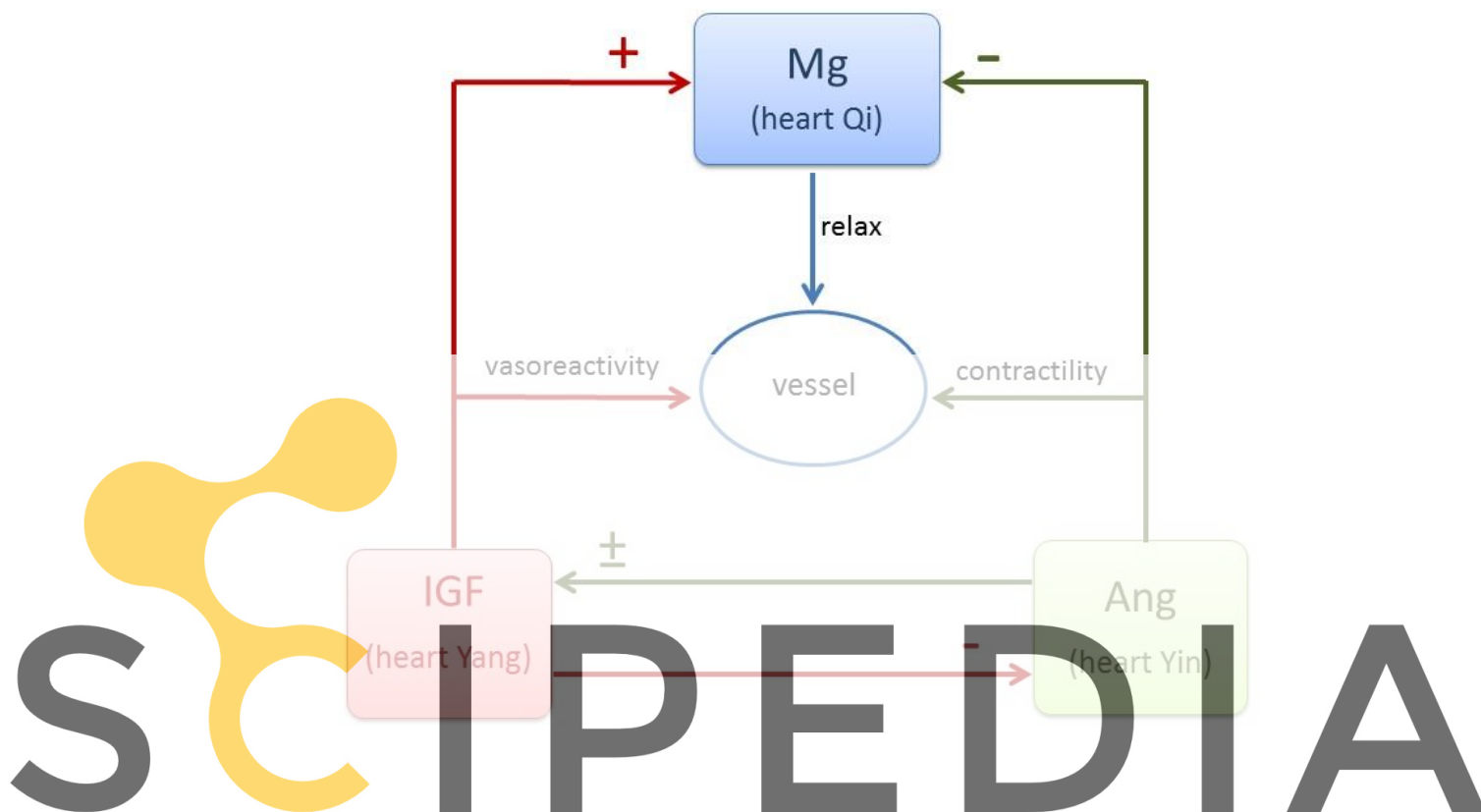


Figure 3. The interrelationship among IGF, Ang and Mg.

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3.2 Key substances of Spleen phase are ANP, aldosterone, retinoic acid, and ghrelin

According to YEIC [1], the Spleen phase should exert significant effect on spleen organ, be generated in heart, govern muscle, and be enlightened in mouth. Moreover, the prosperity of Spleen phase is reflected by lips.

In physiological reality, ANP is secreted by heart muscle cells that intervenes in the short- and long-term control of blood pressure and of water and electrolyte balance [22]. The spleen is an important site of ANP-induced fluid extravasation into the systemic lymphatic system. ANP enhances the extravasation of isoncotic fluid from the splenic vasculature both by raising intrasplenic microvascular pressure and by increasing filtration area [23]. ANP inhibits proliferation and hypertrophy of vascular smooth muscle cells and endothelial cells through cGMP production [24] and plays a physiological role on the modulation of salivary secretion [25]. It has been known that the sebum and color of lips of women are dependent on estrogen [26] and the feature of lips of men is dependent on testosterone [27], moreover, estrogen receptors increase ANP [28] and ANP induces testosterone production [29], indicating that lips reflect the level of ANP. As the famous function of Spleen Yang in TCM is “warming” and

maintaining body temperature is an important function of ANP [30], we identify ANP as Spleen Yang.

Aldosterone retains needed salt in human body and helps control blood pressure, the balance of electrolytes in blood, and the distribution of fluids in the body. An intracardiac production of aldosterone was recently found in rat [31]. Aldosterone increases spleen size and weight [32], and stimulates vascular smooth muscle cell proliferation [33]. Aldosterone is enlightened in mouth, as low level of aldosterone causes dry mouth [34] and aldosterone refreshes mouth [35]. Moreover, estrogen receptor- β ligands modulate aldosterone synthesis [36] and short-term testosterone administration decreases aldosterone levels of men [37], indicating the appearance of lips reflects aldosterone level. Retinoic acid (vitamin A) controls the homeostasis of splenic cells [38] and is generated by the epicardium [39]. It also induces differentiation in both adult skeletal muscle primary satellite cells and a myogenic cell line [40], regulates oral epithelial differentiation [41], and serves as an effective treatment for oral leukoplakia [42]. Moreover, excess exogenous retinoic acid can induce cleft palate [43], indicating it affects the appearance of lips. Since either aldosterone or retinoic acid inhibits heat generation in body [44] [45], we identify them as Spleen Yin.

Ghrelin is a gastric peptide that regulates the distribution and consumption of energy. Ghrelin inhibits proliferation of splenic T cells [46] and modulates cardiac, smooth, and skeletal muscle functions [47]. Ghrelin produced in the oral cavity appears to play a regulatory role in innate immune responses to inflammatory infection [48]. Moreover, estrogen replacement therapy increased active plasma ghrelin levels [49] and testosterone correlates positively with ghrelin levels in men [50], indicating that ghrelin is reflected by the appearance of lips. In TCM, Spleen Qi has the function of delivering and transforming food energy; as ghrelin effectively regulates food intake and energy homeostasis [51], we identify it as Spleen Qi.

Figure 4 shows the contrary effect and supportive relationship between ANP and aldosterone/retinoic acid. ANP has exactly opposite function of aldosterone, ANP decreases circulating aldosterone and vice versa [52]. Retinoic acid signaling markedly stimulates natriuretic peptide receptor-A gene expression [53]. ANP inhibits proliferation of vascular smooth muscle [24], aldosterone stimulates muscle cell proliferation [33] and retinoic acid induces muscle differentiation [40]. Moreover, it was found that ANP level decreases significantly after treatment with ghrelin in a rat model [54]; ghrelin elevates aldosterone [55]; and applying ghrelin supplementation to normal lungs increased retinoic acid receptor α/γ expression [56].

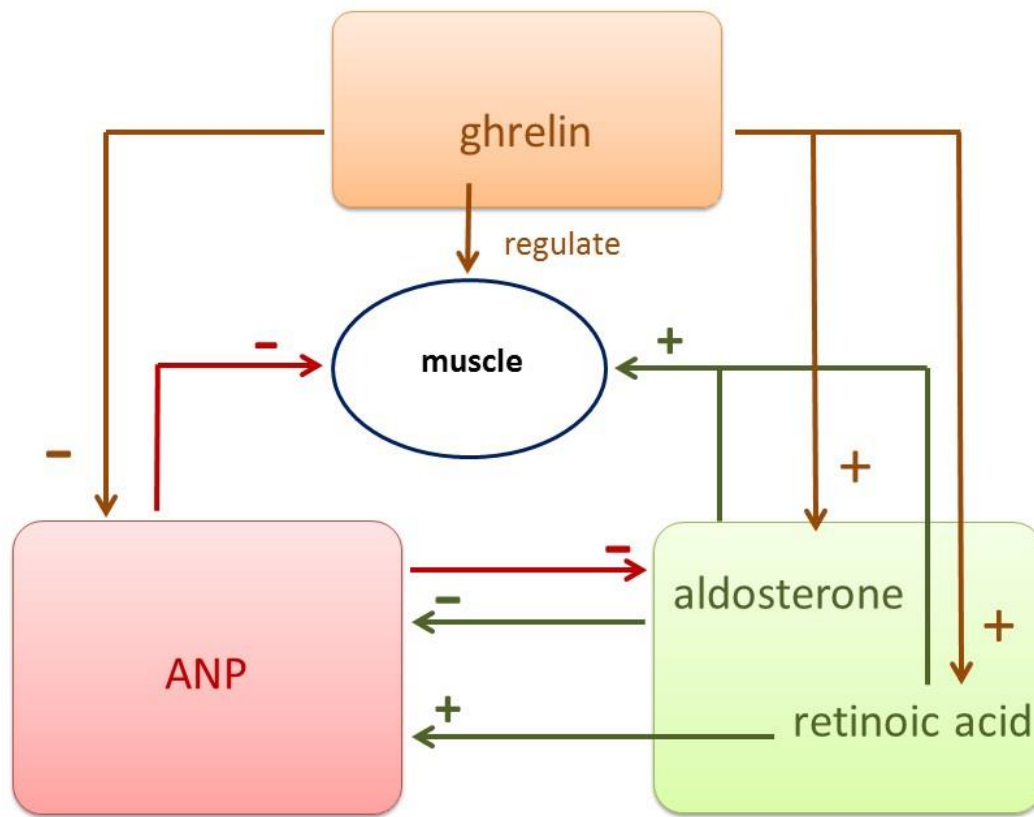


Figure 4. The interrelationship among signaling molecules of Spleen Phase.

3.3 Key substances of Lung phase are FGF7, VEGF, ascorbic acid and HIF

According to YEIC [1], these signaling molecules should exert significant effect on lung organ, be secreted in spleen, govern skin and hair, and be enlightened in nose. Moreover, the prosperity of Lung phase is reflected in body hair.

FGF7 is secreted by spleen [57] and is a potent mitogen that enhances cell proliferation in various organs, including the lung, skin, intestine, breast, and liver. It controls the lung morphogenesis, respiratory epithelial cell differentiation and proliferation [58]. FGF7-treated skin is significantly stronger than control vector-transfected skin, indicating that FGF7 can increase epithelial thickness and strength [59]. FGF7 is expressed in the hair follicle and may have several functions in the hair growth cycle [60]. FGF7 might play an important role in nasal epithelial proliferation and that excessive synthesis of FGF7 in nasal polyp stroma may contribute to hypertrophy of the nasal mucosa in patients with chronic sinusitis associated with nasal polyposis [61]. Due to its proliferation effect, we identify FGF7 as Lung Yang.

VEGF is critical for the development and maintenance of the lung and also plays a role in several acute and chronic lung diseases [62]. It was found that splenic T cells produce VEGF [63]. VEGF is the major mediator of hair follicle growth and cycling that promotes hair growth and increases hair follicle and hair size [64]. VEGF is also the major skin angiogenesis factor [65]. Moreover, VEGF promotes nasal epithelial cell growth and inhibits apoptosis [66]. The platelet-rich plasma injection has been used in the treatment of androgenetic alopecia, it was found that activated platelet-rich plasma prolongs anagen phase of hair growth cycle through increasing FGF7 level and increases the perifollicular vascular plexus through increasing VEGF level [67], indicating that both FGF7 and VEGF affect the appearance of hair. As the function of brown adipose tissue is to generate body heat and VEGF is important for brown adipose tissue development and maintenance [68], we identify VEGF as Lung Yang.

Ascorbic acid (Vitamin C) was identified in the early 1900s in the search for a deficient substance responsible for scurvy which was directly linked to pneumonia. Vitamin C is a physiological antioxidant protecting host cells against oxidative stress caused by infections, and plays a role on preventing and treating pneumonia [69] and other lung disease [70]. It was found that vitamin C content in spleen is much higher than that in other organs [71] and there exists an extracellular pool of ascorbic acid in lung maintained even during scurvy [72]. Dihydrotestosterone (DHT)-dependence causes hair loss, it was found that L-ascorbic acid 2-phosphate, a stable form of vitamin C, represses DHT-induced DKK-1 expression in cultured dermal papilla cells of human hair follicles [73]. Vitamin C is an essential component in producing collagen in body and a potent antioxidant that can help rejuvenate aged and photodamaged skin [74]. Ascorbic acid is also enlightened in nose, as Vitamin C is safe and natural therapies used to treat perennial allergic rhinitis [75]. Moreover, deficiency of ascorbic acid causes enlargement and keratosis of hair follicles mainly of the upper arms [76], indicating that the body hairs reflect the level of ascorbic acid. TCM considers that Lung Yin has “moisturizing lung” effect, therefore we identify ascorbic acid as Lung Yin.

HIF which is a highly conserved transcription factor that is present in almost all cell types, is tightly regulated by oxygen availability, and regulates the expression of hundreds of

genes. HIF system plays a critical role in pulmonary development [77]. HIF-2 α and HIF-1 β are highly expressed in the precortex above the hair matrix, an area containing differentiating stem cells; and HIF-2 α / HIF-1 β complex regulates hair follicle differentiation [78]. Moreover, HIF-1 α plays a crucial role in skin homeostasis and stress response [79] and HIF-1 mediates nasal polypogenesis [80]. Due to its strong regulation function, we identify HIF as Lung Qi.

Figure 5 shows the contrary and regulating interrelationship of HIF, FGF7, VEGF and vitamin C. HIF-1 activates VEGF transcription in hypoxic cells [81]. HIF promotes the expression of FGF7 mRNA levels [82]. Vitamin C prevents endothelial VEGF and VEGFR-2 overexpression [83] and inhibits NO-induced HIF-1 α stabilization and accumulation [84]. Ascorbic acid stimulates collagen synthesis, but FGF inhibits collagen synthesis in the gels [85].

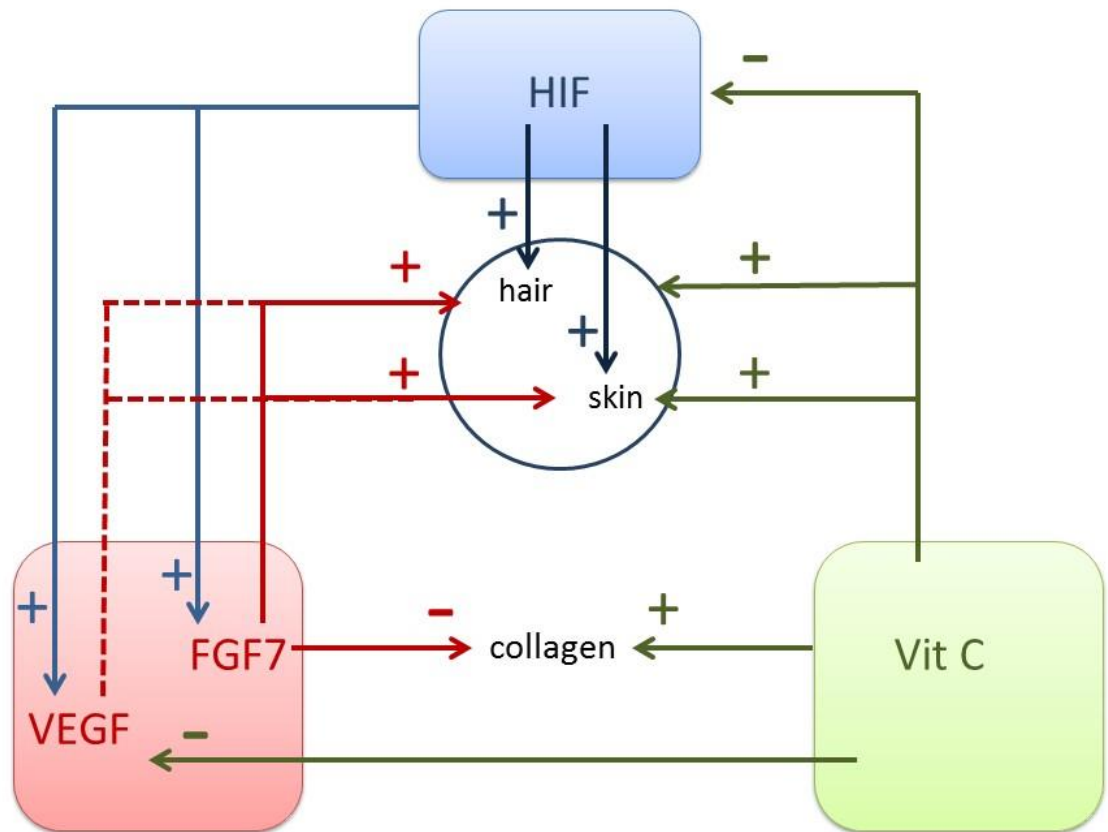


Figure 5. Interrelationship among signaling molecules of Lung Phase.

3.4 Key substances of Kidney phase are calcitonin, PTHrP, Wnt and NO

According to YEIC, Kidney phase should exert significant effect on kidney organ, be generated in lung, govern bone, and be enlightened in ears. Moreover, the prosperity of Kidney phase is reflected in hair.

Both calcitonin and PTHrP are secreted from lung [86] [87]. Calcitonin augments the renal reabsorptive capacity for calcium [88], enhances osteoblastic bone formation, and inhibits bone-resorbing activity of osteoclasts [89]. Calcitonin treatment can stabilize hearing loss or improve hearing in Paget's disease [90]. Moreover, calcitonin gene-related peptide (CGRP) treatment reduces the hair follicle pigmentation [91], indicating the appearance of hair reflects CGRP level. PTHrP is potent renal regulating factor and mitogenic for various renal cell types, and plays a role in renal development [92]. It plays a central role in the physiological regulation of bone formation by promoting recruitment and survival of osteoblasts, and probably plays a role in regulating bone resorption by enhancing osteoclast formation [93]. Moreover, PTHrP mRNA can be detected in the otic vesicle [94]. Furthermore, PTHrP may induce premature catagen-telogen transition in hair growth [95], indicating that PTHrP may affect the appearance of hair. TCM considers that the important function of Kidney Yang is “warming”, as both calcitonin and PTHrP have “warming” effect [96]; [97], we identify both calcitonin and PTHrP as Kidney Yang.

Wnt signaling regulates cell-to-cell interactions during development and adult tissue homeostasis, and is associated with kidney development and kidney diseases [98]. Several Wnt genes are expressed in lung [99]. Wnt signaling has potential roles in bone remodeling in both physiological and pathological conditions, it acts on osteoblast precursor cells and promote their differentiation into mature osteoblasts, and it can either suppress bone resorption or enhance osteoclast formation through various signaling pathway [100]. Wnt is also enlightened in ears, as Wnt signaling is active in dorsal regions of the otic vesicle, where it functions to regulate the expression of genes (Dlx5/6 and Gbx2) necessary for vestibular morphogenesis [101]. Wnt signaling is a key pathway that initiates pigmented hair regeneration [102], indicating the appearance of hair reflects Wnt level. Since Wnt signaling blocks thermogenesis [103], we identify Wnt as Kidney Yin.

NO is the second messenger and a major regulator in the cardiovascular, immune, and nervous systems. In the kidney NO has numerous important functions including the regulation of renal hemodynamics, maintenance of medullary perfusion, mediation of pressure-natriuresis, blunting of tubuloglomerular feedback, inhibition of tubular sodium reabsorption, and modulation of renal sympathetic neural activity [104]. It is found that both osteoclasts and osteoblasts have inducible NO synthase and produce NO, whereas NO inhibits the proliferation of osteoclasts and decreases the proliferation of osteoblasts [105]. NO also plays an important role in the inner ear to regulate physiological reactions in both cochlea and vestibular parts of the labyrinth [106]. Moreover, NO regulates hair follicle activity [107], indicating that NO would affect the appearance of hair. Due to its strong regulation function, we identify NO as kidney Qi.

Figure 6 shows the interrelationships among calcitonin, PTHrP, Wnt and NO. Calcitonin stimulates expression of sclerostin [108] which is an inhibitor of Wnt, and administration of PTHrP can increase Wnt signaling [109]. Moreover, calcitonin increases plasma NO levels [110], PTHrP activates NO release [111], and Wnt-5a increases NO production [112]. Calcitonin

enhances osteoblastic bone formation and inhibits bone-resorbing activity of osteoclasts [89]. PTHrP promotes recruitment and survival of osteoblasts and enhances osteoclast formation [93]. Wnt signaling stimulates osteoblastogenesis [113] and decreases osteoclast formation [114].

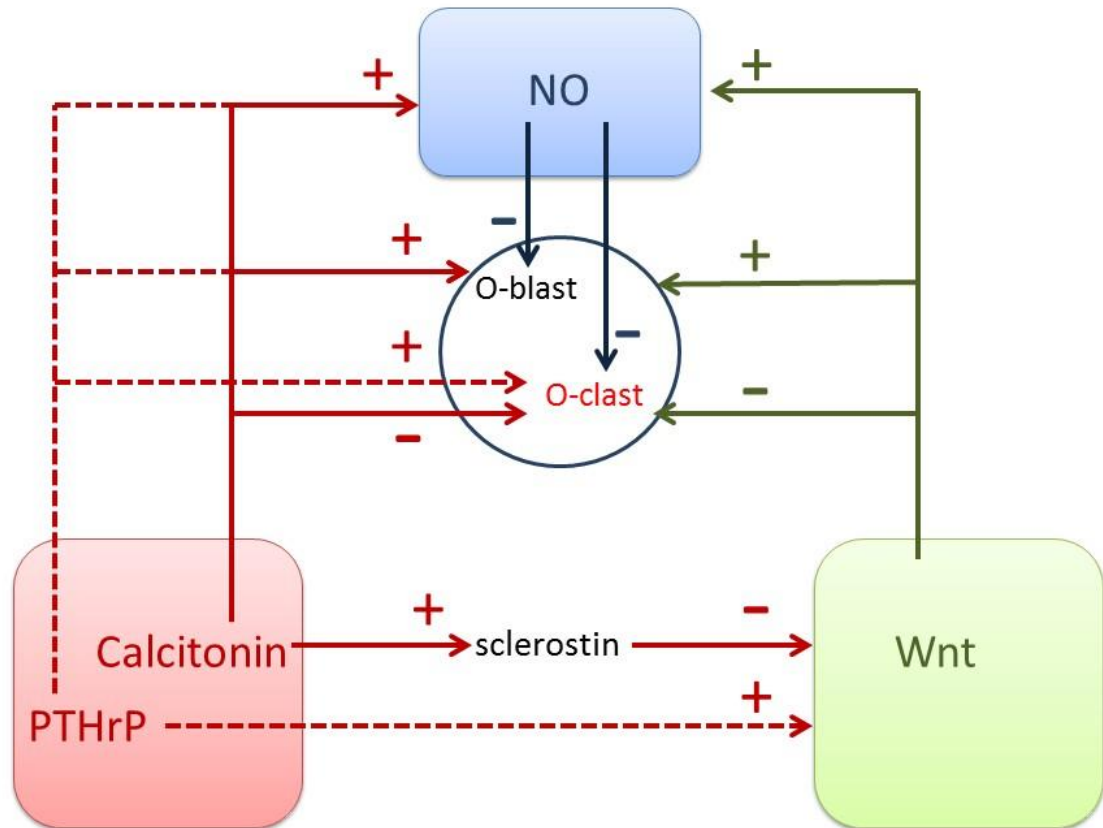


Figure 6. The interrelationship among signaling molecules of Kidney Phase.

3.5 Key substances of Liver phase are EPO, HGF, renin, SOD, AKR, and GSH

According to YEIC, Liver phase should exert significant effect on liver organ, be generated in kidney, govern tendon, and be enlightened in eyes. Moreover, the prosperity of Liver phase is reflected in “paw” (finger, toe, nail).

EPO is a glycoprotein that promotes the proliferation and differentiation of erythrocyte precursors. It was reported that high-dose EPO increases liver regeneration by affecting the biochemical, morphological, and histopathological parameters after liver resection [115]. EPO is produced principally in the liver during fetal gestation and mainly in the kidney for adult [116]. It is used to provide protective and regenerative activity in non-haematopoietic tissues and stimulates tendon healing [117]. EPO is a potent angiogenic factor observed in the diabetic human and mouse eyes [118]. Moreover, digital clubbing is defined by structural changes at the base of the nails which is associated with increased EPO levels [119], and patients using

erythropoiesis stimulating agents have lower rate of onychomycosis compared to those not using them [120], indicating that the appearance of finger reflects the EPO level. Since EPO increases brown fat gene expression [121] and has proliferation effect, we identify EPO as Liver Yang.

YEIC also denotes that Kidney Phase produces bone, and bone produces Liver Phase [1]. HGF is produced by mesenchymal cells, and the bone marrow stem contains mesenchymal stem cells. HGF accelerates both the hepatic regeneration and function in vivo [122]. Platelet-rich plasma containing HGF is widely used in orthopaedic/sports medicine to repair injured tendons [123] and local administration of recombinant HGF promotes the adhesive healing process at the tendon-bone junction both histologically and mechanically [124]. HGF is also enlightened in eyes. There is growing evidence that HGF is synthesized by autocrine loops in a number of cell systems prominent among which are ocular cells such as the corneal endothelium, the lens epithelium, the retinal pigment epithelium and others; furthermore, HGF is a constituent of tears, aqueous humour and vitreous humour [125]. Moreover, digital clubbing is stimulated by high level of HGF [126], indicating that the appearance of fingers reflects the HGF level. As HGF plays a central role in adipose tissue development [127] and has proliferation effect, we identify HGF as Liver Yang.

Renin is produced in kidney and exerts significant effect on liver. The renin-substrate concentration in patients with liver disease is much lower than that of normal subjects [128]. Loading-induced periodontal ligament tissue homeostasis is regulated through the renin–angiotensin system [129]. Renin is also present in human eyes [130]. Moreover, the psoriasis usually affects the fingernails and toenails, causing pitting, thickening, and irregular contour of the nail; it was found that plasma renin activity was enhanced in psoriatic patients [131], indicating that renin would affect the appearance of nails. As blockade of the renin-angiotensin system improves liver regeneration [132], we identify renin as Liver Yin.

SOD is an important antioxidant defense in nearly all living cells exposed to oxygen and is intensively expressed in kidney [133]. SOD mimetic improves the function, growth and survival of small size liver grafts after transplantation in rats [134] and Cu/Zn SOD is broadly distributed in liver [135]. Mn-SOD is excessively expressed in the cultured fibroblasts derived from the stress-deprived patellar tendon in the rat [136]. SOD is also enlightened in eyes. The retina contained much CuZn-SOD activity and the cornea and sclera contained several times more SOD activity than the lens [137]. Moreover, the levels of MnSOD are reduced in psoriasis [138], indicating that SOD would affect the appearance of nails. It was found that cold-exposure activates brown adipose tissue thermogenesis but decreases SOD expression [139], indicating SOD has “cooling” effect, therefore we identify SOD as Liver Yin.

AKR is expressed in kidney [140]. The AKR superfamily comprises of several enzymes that catalyze redox transformations involved in intermediary metabolism, detoxification and biosynthesis [141]. AKR-7A protects liver cells and tissues from acetaminophen-induced oxidative stress and hepatotoxicity [142]. It was found that the AKR content is much higher in patients with tendon xanthomas, indicating that AKR plays important role in tendon [143]. AKR is also enlightened in eyes, as expression of both AKR1B1 and AKR1B10 can be observed in cornea, iris, ciliary body, lens, and retina [144]. Cold-exposure suppresses AKR level significantly [145], indicating AKR has “cooling” effect, therefore we identify AKR as Liver Yin.

GSH is a substance produced naturally by the liver and effectively scavenges free radicals and other reactive oxygen species [146]. GSH plays a key role in the liver in detoxification reactions and has close relationship with tendon and eyes. It was reported that GSH level was significantly decreased in post-injury chicken models and increasing GSH can reduce the extent of adhesion of healing tendons [147]. GSH and the related enzymes belong to the defense system protecting the eye against chemical and oxidative stress; ageing, cataract, diabetes, irradiation and administration of some drugs could cause changes of GSH and related enzymes activity in lens, cornea, retina and other eye tissues [148]. Moreover, nail hyperpigmentation involves decreased GSH levels [149], indicating the appearance of nail reflects the GSH level. In TCM, Liver Qi has “catharsis” function; due to its strong detoxification effect, we identify GSH as Liver Qi.

Figure 7 shows the interrelationships among EPO, HGF, renin, SOD, AKR and GSH. HGF raises cellular GSH levels as well as SOD1 expression [150] [151], and downregulates aldose reductase [152] which is the prototypical enzyme of the AKR superfamily [153]. When treated with EPO, the GSH and SOD levels in kidney of rats are significantly decreased [154]. The extracellular SOD is a major repressor of hypoxia-induced EPO gene expression [155], but treatment with EPO increases vascular expression of SOD1 [156]. SOD and GSH work together to prevent or repair the damage caused by reactive oxygen species. SODs convert superoxide radical into hydrogen peroxide and molecular oxygen, while the GSH peroxidases (GPx) convert hydrogen peroxide into water, and GSH helps the productivity of GPx [157]. GSH and AKR are also interrelated, since GSH levels are reduced in AKR-deficient strains [158]. Furthermore, renin-angiotensin system stimulates EPO secretion [159], blockade of the renin-angiotensin system enhances hepatic HGF production [160], and inhibition of GSH increases plasma renin activity [161].

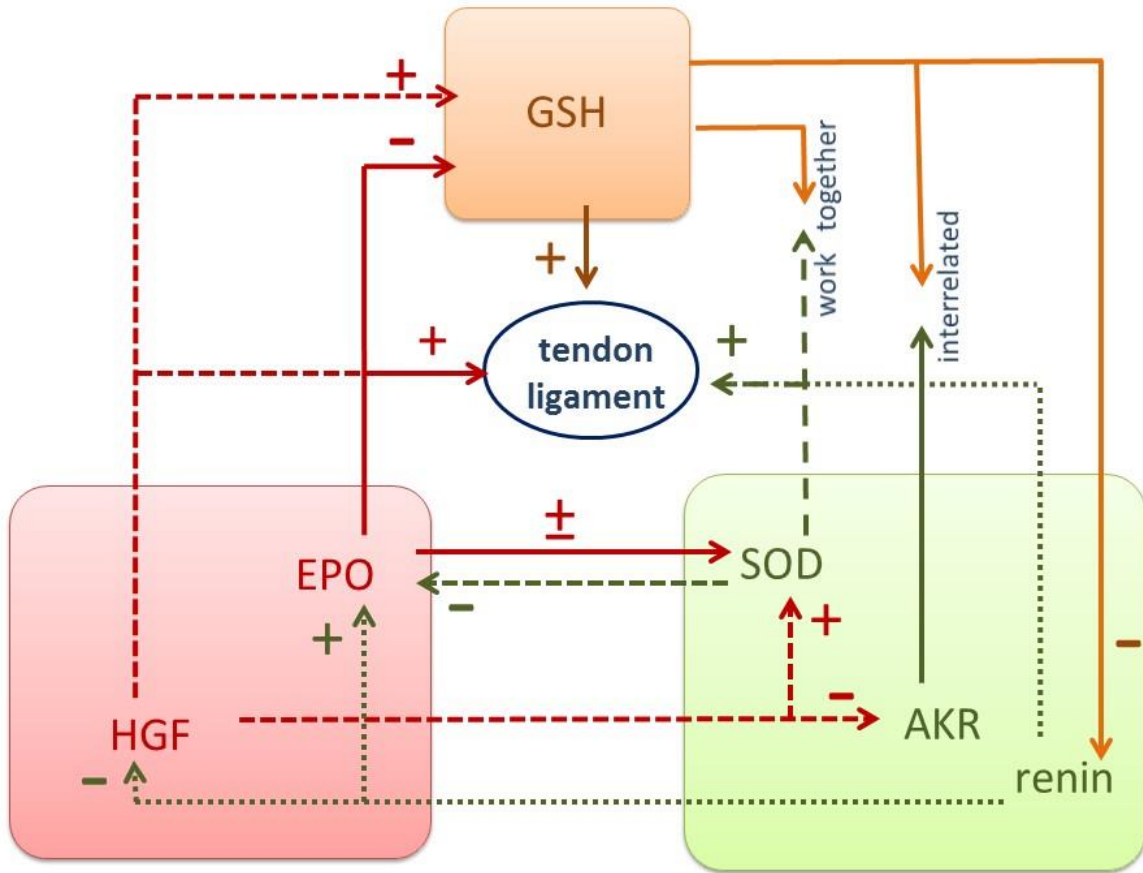


Figure 7. The interrelationship among signaling molecules of Liver Phase.

4. The consistency between pathways of signaling molecules and Five Phases in TCM

Figure 8 shows that the signaling molecules corresponding to Yang-Yin-Qin within the same phase regulate each other (Supplementary Information), and the pathways of signaling molecules among different phases are consistent with the dialectical relationships of Five Phases in TCM.

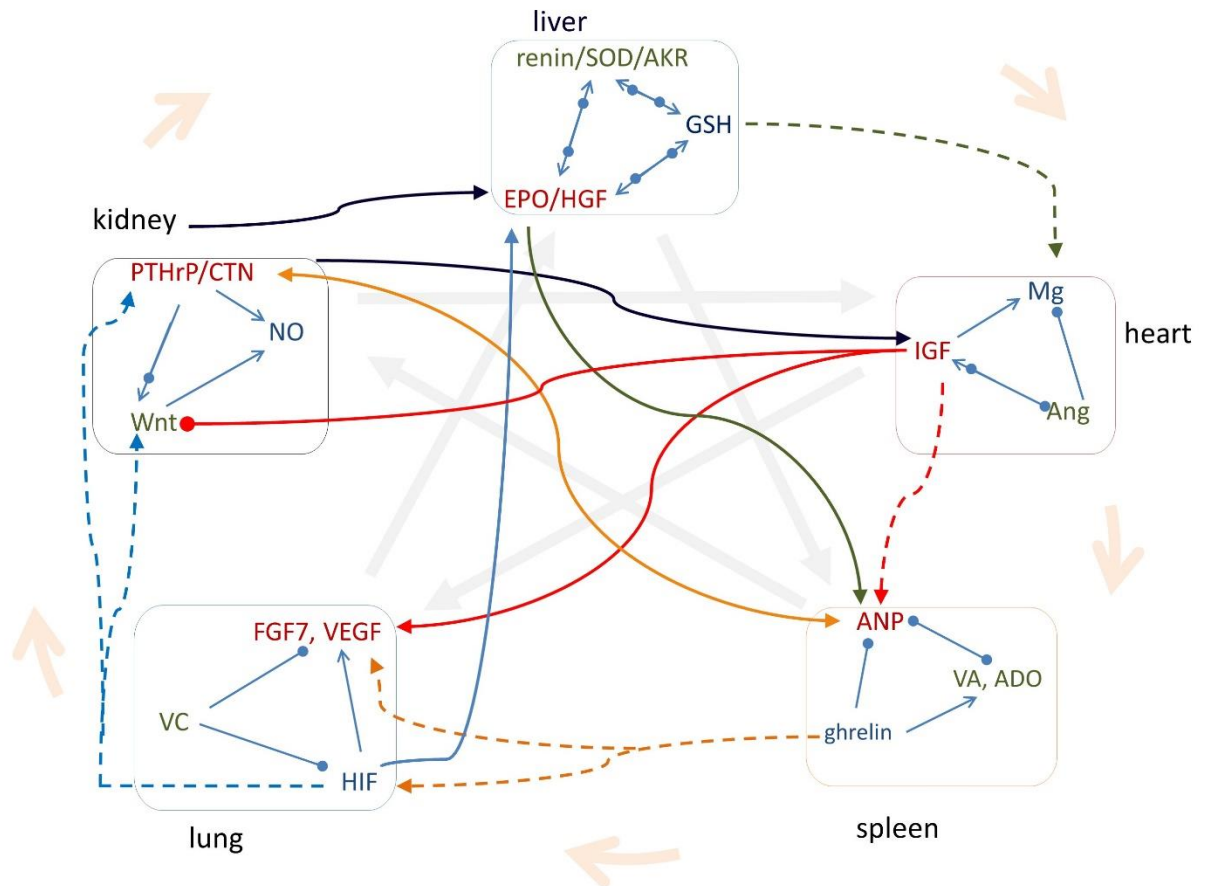


Figure 8. The interrelationship among signaling molecules. Arrow is for assisting and solid circle is for inhibiting.

In Figure 1, the five arrows along the diagonal direction denote the “master-servant” relationships. We show that each relationship is consistent with the pathway of signaling molecules. YEIC states that Spleen phase is subjected to Liver phase. “Yellow Emperor’s

Classic on 81 Medical Problems”, another fundamental doctrinal source for Chinese medicine on therapeutic strategies, states that the disease in liver transfers to spleen, to treat the disease in liver, the best physician should enhance Spleen phase, and then the disease in liver would be recovered [162]; in physiological reality, circulating retinoic acid concentrations are lower in subjects with nonalcoholic fatty liver disease and are associated with hepatic lipid metabolism [163], and ghrelin treatment increases GSH levels [164] and activity of SOD [165]. Moreover, EPO stimulates ANP secretion [166].

YEIC denotes that Kidney phase is subjected to Spleen phase. The popular guidance in TCM therapy stated that Kidney phase is dependent on Spleen phase and vice versa [167]; in physiological reality, ANP increases calcitonin gene-related peptide (CGRP) within human circulation [168] and CGRP stimulates ANP secretion [169].

YEIC denotes that Heart phase is subjected to Kidney phase. The popular guidance in TCM therapy stated that Heart phase and Kidney phase are in harmony, to enhance Heart phase, one should strengthen Kidney phase; to enhance Kidney Yin, one should lower down Heart Yang [170]. In physiological reality, calcitonin increases concentration of IGF [171], and IGF signaling antagonizes the Wnt pathway [172].

YEIC denotes that Lung phase is under the dominion of Heart phase. In physiological reality, magnesium deficiency contributes to pulmonary complications [173]; IGF-1 induces lung fibroblast activation [174]; IGF-1 induces VEGF [175], exogenous administered FGF7 cDNA causes increases in IGF-1 [176], and the combination of IGF-1 and FGF7 cDNA significantly improves dermal and epidermal regeneration [177]; and Ang II increases FGF7 mRNA levels [178] and stimulates VEGF synthesis [179].

YEIC denotes that Liver phase is subjected to Lung phase. In physiological reality, it was found that FGF7 promotes liver regeneration [180]; VEGF promotes proliferation of hepatocytes through reconstruction of liver sinusoids by proliferation of sinusoidal endothelial cells [181]; vitamin C deficiency promotes fatty liver disease development [182] and vitamin C plus E combination treatment is a safe and effective treatment option in patients with fatty liver disease [183]; and HIF plays a role across a range of hepatic pathophysiology [184]. Moreover, VEGF is crucial for EPO-induced improvement of cardiac function [185]; vitamin C elevates red blood cell glutathione in healthy adults [186]; HIF induces EPO production [187] and induction of HIF-1 varies with the GSSG/GSH ratio [188]; FGF-7 stimulates HGF mRNA and protein expression in ovarian surface epithelium [189].

The five arrows along the outer circle in Figure 1 denote the “mother-son” relationships. The signaling molecule corresponding to Yang in each phase is secreted/generated in “mother” organ (Supplementary Information). Moreover, the popular guidance in TCM therapy stated that “Liver and kidney have the same origin and they should be treated together” [190]; in physiological reality, EPO is produced principally in the liver during fetal gestation and in the kidney after birth, and in response to anemia, EPO gene transcription is markedly induced in the kidney and liver [191].

For the relationship of Lung and Spleen phases, TCM stated that “to treat lung disease, one should treat spleen, as Spleen phase can promote Lung phase” [190], and the popular TCM therapy strategy of enhancing Lung Qi is to enhance Spleen phase; in physiological reality, HIF-1 α and VEGF mRNAs are significantly increased after ghrelin administration [192]; retinoic acid increases HIF-1 α [193] and markedly stimulates FGF7 expression [194].

TCM considers that Lung phase and Kidney phase are mutually promoted, and the Kidney Yin can be increased by enhancing lung Qi [170]. In physiological reality, HIF modulates Wnt/ β -catenin signaling [195], induces PTHrP [196], and is regulated by NO [197]; Wnt activates FGF7 during epidermal stratification [198], and regulates vitamin C biosynthesis [199]; and vitamin C increases nitric oxide synthase activity [200].

TCM denotes that Liver phase increases Heart phase, in physiological reality GSH enhances intracellular Mg both in vivo and in vitro [201]. Moreover, Heart phase enhances Spleen phase in TCM, and it was found that IGF-II increases the protein level of ANP [202] (Figure 8).

5. Effects of TCM herbal medicines on signaling molecules

TCM herbal medicines are categorized into various functions to regulate Yang-Yin-Qi in each organ. We now validate our results by exploring whether the Chinese herbal medicine can regulate the corresponding signaling molecules. Table 2 lists some representative herbal medicines and their function on the corresponding signaling molecules.

Ginseng is a famous TCM herbal medicine which can strengthen Spleen phase particularly in enhancing Spleen Qi and benefit Lung phase particularly in augmenting Lung Qi [203]. In physiological reality, ginseng increases ANP level [204] and enhances the ability of all-trans retinoic acid (ATRA) to induce terminal differentiation of leukemia cell [205]; ginsenoside Rb1 significantly stimulates the ghrelin endocrine to inhibit endothelial injury [206]. Ginsenoside-Rg1 effectively relieves aldosterone-induced oxidative stress, thereby indirectly inhibiting aldosterone-induced podocyte autophagy [207]. In human keratinocyte cultures, ginsenoside Rb1 enhances VEGF production and significantly increases expression of HIF-1 α [208].

Astragalus is a popular TCM herbal medicine used to enhance Lung Qi and Lung Yang and increase Spleen Yang [203]. In physiological reality, flavonoids from radix astragali increase the expression of HIF-1 α in both mRNA and protein markedly [209] and enhance VEGF mRNA expression [210]. Furthermore, astragalus induces the natriuresis by significantly improving the renal reaction to ANP [211].

Deer antler is a famous Chinese herbal medicine for strengthening Kidney Yang and benefiting blood, and it principally affects Kidney and Liver phases [203]. In physiological reality, deer antler contains plenty of calcitonin and PTHrP, calcitonin content increases significantly during the rapid antler growth period [212], and intense and overlapping expression of PTHrP and its receptor exists in developing osseocartilaginous structures and in the underlying layers of velvet epidermis of deer antler [213]. Furthermore, deer antler increases serum EPO value [214], SOD activity in serum [215], and glutathione peroxidase [216], which is consistent with that deer antler benefits Liver phase.

In TCM, cynomorium songaricum has the function to warm Kidney Yang and nourish the Liver Yin [217]. In physiological reality, cynomorium songaricum significantly increases calcitonin [218] and increases CuZn-SOD and glutathione peroxidase [219].

Angelica sinensis is famous for enhancing hematopoiesis, and it principally affects Liver and Heart phases [203]. In physiological reality, angelica stimulates EPO to enhance hematopoiesis [220]; [221], promotes HGF [222], increases GSH [223], enhances the activity of SOD [224], and regulates renin activities [225]. Moreover, angelica sinensis polysaccharides stimulates IGF-1 expression [226] but inhibits Ang II [225].

In TCM, cordyceps sinensis is famous to moderately enhance Lung phase [203]. In physiological reality, cordyceps sinensis up-regulates the expression of HIF-1 α [227], maintains higher HIF-1 level in human lung epithelial cells [228], contains higher ascorbic acid contents [229], and lowers VEGF level in lung [230].

In TCM, Lilium lancifolium is famous to nourish Lung Yin [203]. In China, Lilium lancifolium is used as an edible lily and is an important source of ascorbic acid [231].

In TCM, wolfberry (*lyceum barbarum*) is famous to nourish Kidney Yin and Liver Yin [203]. In physiological reality, wolfberry phytochemicals activate Wnt signaling [232], and increase SOD and GPx in blood [233].

TCM formula is a combination of herbs with suitable dosage to treat symptoms, and some formulas are particularly used to regulate Yang-Yin-Qi of organs. Table 3 lists some representative TCM formulas and shows that these TCM formulas regulate the corresponding signaling molecules. Liujunzi Tang (Six Gentlemen Decoction, consisting of ginseng, bighead atractylodes rhizome, poria, roasted licorice root, tangerine peel and pinellia tuber) is used to replenish Spleen Qi [234], it is widely used for the treatment of the upper gastrointestinal symptoms of patients with functional dyspepsia, gastroesophageal reflux disease, dyspeptic symptoms of postgastrointestinal surgery patients, and chemotherapy-induced dyspepsia in cancer patients, and oral administration of Liujunzi Tang potentiates orexigenic action of ghrelin [235].

Yiguan Decoction (consisting of glehnia root, ophiopogon root, Chinese angelica root, dried rehmannia root, wolfberry, Sichuan chinaberry) is used to nourish Liver Yin and soothe Liver Qi in TCM [234]. It was found that Yiguan Decoction significantly increases protein expressions of Cu/Zn SOD, glutathione S-transferase (GST) and AKR family 7, while notably decrease the expression of glutathione synthetase (GSS) [236].

Liuwei Dihuang Wan (Rehmannia Bolus with Six Herbs, consisting of prepared rhizome of rehmannia, dogwood fruit, dried Chinese yam, oriental water plantain, poria, moutan bark) is used to nourish and enrich Kidney Yin in TCM [234]. In physiological reality, it could up-regulate canonical Wnt/beta-catenin signaling [237].

Zuogui Pill (Back to Left Pill, consisting of prepared rhizome of rehmannia, the seed of Chinese dodder, achyranthes bidentate, glue of tortoise plastron, deerhorn glue, Chinese yam, dogwood fruit, and wolfberry) is used to nourish Kidney Yin in TCM [238], and it was found that Zuogui Pill increases Wnt1 in Wnt signal transduction pathway [239].

ShenQi Pill (Kidney Qi Pill, consisting of dried rehmannia root, Chinese yam, dogwood fruit, oriental water plantain, poria, moutan bark, cinnamon twig, and prepared aconite root) is used to enhance Kidney Qi [234]. In physiological reality, it can significantly increase NO production [240].

Zonghai Tang [1851-1908] was a famous Chinese physician, he stated that “replenishing Spleen Yin is for appetite” [241]; to replenish spleen Yin, he suggested to use “Mai-men-dong Tang” (Ophiopogon Japonicus Decoction) formulated by Jing-Yue Zhang (1563-1640) [167]. Ophiopogon Japonicus Decoction consists of ophiopogon japonicus and japonica rice, in which ophiopogon japonicus contains vitamin A [203]. In China, japonica rice grows up in temperate region, it was found that temperate japonica rice has the highest levels of carotenoids among the types of rice [242], and carotenoids are a group of plant pigments important in the human diet as the only precursors of vitamin A [243].

Table 2.

Consistence between effects of Chinese herbal medicine on TCM functions and on signaling molecules.

herbal medicine	TCM functions	effect on signaling molecules
ginseng	↑Spleen phase [203]	↑ANP[204], ↑ATRA[205], ↑ghrelin[206], ↓aldosterone[207]
	↑Lung phase[203]	↑VEGF, ↑HIF [208]
astragalus	↑Lung Qi,	↑HIF [209]
	↑Lung Yang [203]	↑VEGF [210]
	↑Spleen Yang [203]	↑ANP [211]
deer antler	↑Kidney Yang [203]	contain calcitonin & PTHrP [212, 213]
	benefit blood, affect Liver phase [203]	↑EPO[214], ↑SOD[215], ↑GSH px[216]
cynomorium songaricum	warm Kidney Yang [217]	↑calcitonin [218]
	nourish Liver Yin [217]	↑SOD, ↑GSH px [219]
angelica sinensis	↑ hematopoiesis, affect LIVER	↑EPO[220, 221], ↑HGF[222], ↑GSH[223], ↑SOD[224], ↑↓ renin[225]
	affect HEART [203]	↑IGF[226], ↓ Ang II [225]
cordyceps sinensis	↑Lung phase[203]	↑HIF[227, 228], ↑ascorbic acid[229], ↓VEGF[230]
lilium lancifolium	nourish Lung Yin[203]	Contain ascorbic acid[231]
wolfberry	↑ Kidney Yin and Liver Yin[203]	↑ Wnt[232], ↑ SOD, ↑ GSH px[233]

Table 3.

Consistence between effects of TCM formula on TCM functions and on signaling molecules.

TCM formula	TCM functions	effect on signaling molecules
Liujunzi Tang (Six Gentlemen Decoction)	↑Spleen Qi [234]	↑ ghrelin [235]
Yiguan Decoction	↑ Liver Yin	↑ SOD, ↑ AKR [236]
	sooth Liver Qi [234]	↑ GST, ↓ GSS [236]
Liuwei Dihuang Wan (Rehmannia Bolus with Six Herbs)	↑Kidney Yin [234]	↑ Wnt [237]
Zuogui Pill (Back to Left Pill)	↑ Kidney Yin[238]	↑ Wnt [239]
Shenqi Pill (Kidney Qi Pill)	↑Kidney Qi [234]	↑ NO [240]
Mai-Men-Dong Tang (Ophiopogon Japonicus Decoction)	↑ spleen Yin [241]	↑ vitamin A [203, 242, 243]

6. The consistency between pathways of signaling molecules and eight TCM treatment principles

TCM developed eight popular treatment principles [244]. We compared these eight treatment principles with the pathways of corresponding signaling molecules, and found that these eight principles precisely described the molecular signaling, as shown in Figure 9.

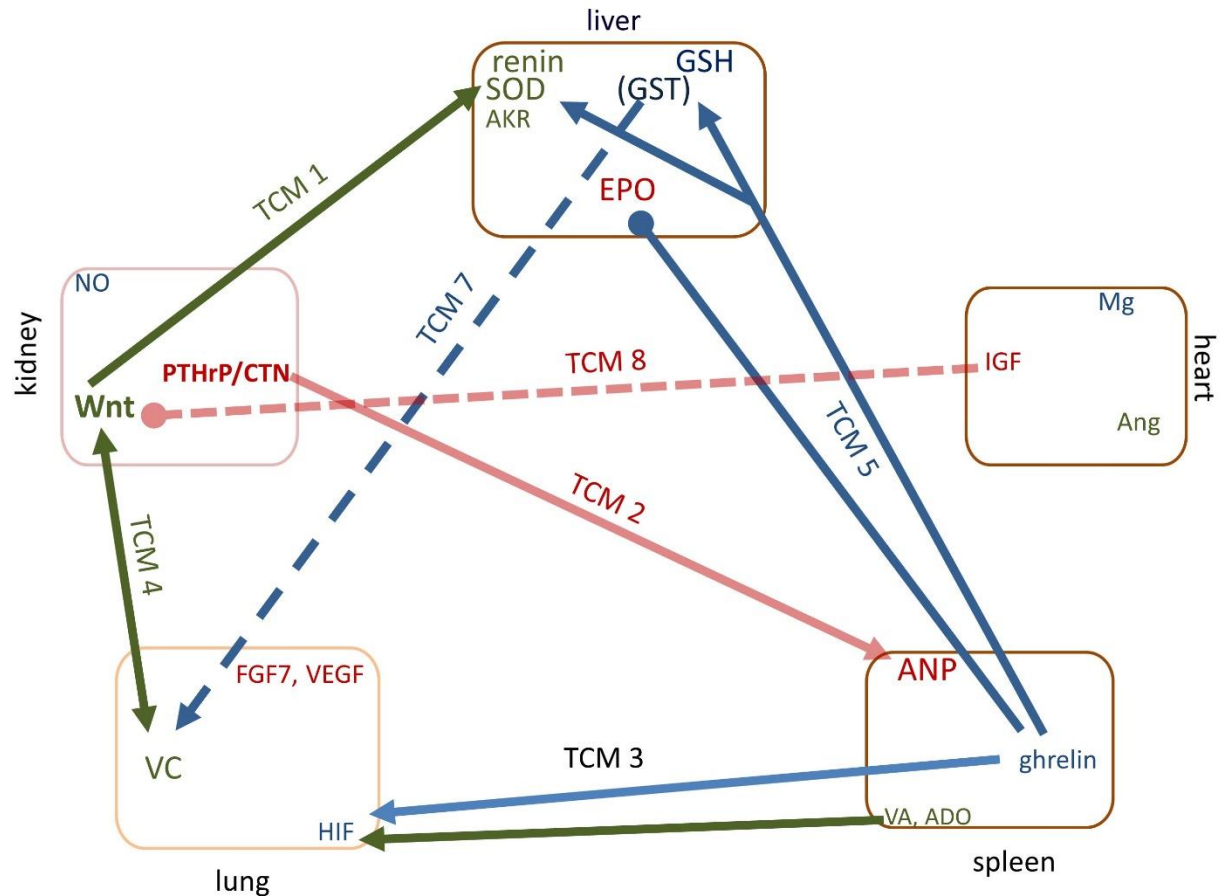


Figure 9. The consistence between eight TCM treatment principles and pathways of signaling molecules. TCM 1: replenishing kidney Yin then replenishing liver Yin; TCM 2: warming kidney Yang to replenish spleen Yang; TCM 3: strengthening spleen to replenish lung Qi; TCM 4: lung Yin and kidney Yin assisting each other; TCM 5: invigorating spleen and dredging liver; TCM 7: replenishing lung Yin and cleansing liver; TCM 8: reducing heart Yang to replenish kidney Yin. Arrow indicates increasing, and solid circle indicates decreasing.

The first TCM treatment principle is “replenishing kidney Yin then replenishing liver Yin” which is usually used for kidney Yin deficiency and liver Yin insufficiency [244]. In physiological reality, the up-regulation of Wnt/ β -catenin signaling is associated with the recovery of SOD levels [245], Wnt/ β -catenin is the master regulator that controls multiple renin-angiotensin system genes [246], and SOD1 overexpression can restore impaired Wnt signaling

[247], indicating that the Wnt (kidney Yin molecule) and renin/SOD (liver Yin molecules) are assisting each other. Therefore, this TCM method describes accurately the relationship of molecular signaling.

The second TCM treatment principle is “warming kidney Yang to replenish spleen Yang” which is used for declined kidney Yang induced weak spleen Yang [244]. In physiological reality, calcitonin gene-related peptide (CGRP) stimulates ANP secretion [169], indicating that increasing CGRP (kidney Yang related molecule) would stimulates ANP (spleen Yang molecule).

The third TCM treatment principle is “strengthening spleen to replenish lung Qi” which is used for declined spleen Qi induced lung Qi debility [244]. In physiological reality, HIF-1 α and VEGF mRNAs are significantly increased after ghrelin administration [192], and retinoic acid increases HIF-1 α [193]. Therefore, increasing ghrelin (spleen Qi molecule) and retinoic acid (spleen Yin molecule) could enhance HIF (lung Qi molecule).

The fourth TCM treatment principle is “lung Yin and kidney Yin assisting each other” which is used for the cases of deficient kidney Yin induced lung Yin deficiency, or deficient lung Yin induced kidney Yin deficiency[244]. In physiological reality, Wnt regulates vitamin C biosynthesis [199]; treatment with ascorbic acid treatment can improve the effect of Wnt signaling [248], indicating that Wnt (kidney Yin molecule) and ascorbic acid (lung Yin molecule) assist each other.

The fifth TCM treatment principle is “invigorating spleen and dredging liver” [244]. Liver Qi molecule is glutathione which exists in both reduced GSH and oxidized GSSG states. As shown in Figure 10, in the glutathione redox cycle, GSH is converted by glutathione peroxidase (GPx) to GSSG; GSH can be regenerated from GSSG by the enzyme glutathione reductase (GR). Mitochondrial Glutathione-S-transferases (GSTs) display both GSH transferase and peroxidase activities that detoxify harmful byproducts through GSH conjugation or GSH-mediated peroxide reduction [249]. In physiological reality, ghrelin treatment can decrease plasma EPO and EPO gene expression in the hypoxic rats [250], and increase SOD, GPx, GST, GR and GSH [251, 252], indicating ghrelin treatment (spleen Qi molecule) can enhance the glutathione redox cycle, i.e., dredge liver.

The sixth TCM treatment principle is “invigorating spleen for diuresis (reducing edema)” [244]. In physiological reality, ghrelin (spleen Qi molecule) promotes diuresis [253, 254], administration of ghrelin may be useful in reducing brain edema induced by acute systemic hypoxia [255], increased levels of aldosterone (spleen Yin molecule) are able to maintain sodium balance and avoid an edematous state [256], and 9-cis retinoic acid (spleen Yin molecule) could significantly prevent postsurgical lymphedema [257].

The seventh TCM treatment principle is “replenishing lung Yin and cleansing liver” [244]. In physiological reality, GST has the ability to catalyze the conjugation of GSH to xenobiotic substrates for the purpose of detoxification; GST improves the serum ascorbic acid response to vitamin C intake [258], and GST enzymes protect against serum ascorbic acid deficiency when dietary vitamin C is insufficient [259]. This indicates that “detoxification” (cleansing liver) improves the serum ascorbic acid response (lung Yin).

The eighth TCM treatment principle is “reducing heart Yang to replenish kidney Yin” which is used for vigorous heart Yang induced kidney Yin deficiency [244]. In physiological

reality, IGF signaling antagonizes the Wnt pathway [172], i.e., one should decrease IGF (heart Yang) for increasing Wnt signaling (kidney Yin).

Therefore, the eight classic TCM treatment principles are highly consistent with the pathways of corresponding signaling molecules.

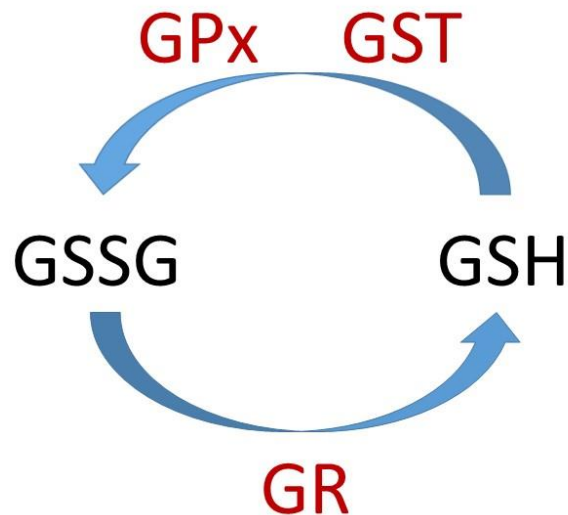


Figure 10. The glutathione redox cycle. GSH is the reduced state and GSSG (glutathione disulfide) is the oxidized state. GSH is converted by glutathione peroxidase (GPx) to GSSG; GSH can be regenerated from GSSG by the enzyme glutathione reductase (GR). Glutathione-S-transferase (GST) GST can catalyze the conjugation of GSH for detoxification.

7. The modern medicine and TCM could identify the same pathogenesis of diseases

With the direct mapping, we can demonstrate that TCM and modern medicine actually identify the same pathogenesis of human disease and apply the same treatment strategy. TCM considers that heart is connected with small intestine. Yuan-fang Chao (550-630) was a famous imperial doctor in Chinese history, he stated that “As heart is connected with small intestine, if heart has excess heat (excess Heart Yang), then the heart heat stagnates at small intestine and results in hematuria” [260], and the effective TCM treatment strategy is to lower the Heart Yang (or IGF). In physiological reality, IGF-1 level was higher in Henoch-Schönlein purpura patients with hematuria than in controls [261], and the angiotensin-converting enzyme inhibitor can effectively treat gross hematuria [262]. As angiotensin-converting enzyme inhibitor therapy significantly reduces circulating IGF-1 [263], this treatment strategy of modern medicine is the same as that of TCM.

TCM considers that spleen is connected with stomach. Dong-yuan Li (1180-1251), a Chinese physician famous in the relationship between spleen and stomach, stated that raising Spleen Yang (or ANP) could benefit stomach [264]. In physiological reality, endogenous ANP stimulates somatostatin secretion from antrum of human stomach, and stimulation of somatostatin secretion is coupled to inhibition of gastrin secretion in the antrum [265]. Moreover, ghrelin stimulates gastric motility [266].

TCM considers that lung is connected with large intestine. Zonghai Tang (1851-1908) stated that “Lung Yang moves heat to large intestine thus make it stagnated, and insufficient Lung Yin (or vitamin C) results in constipation” [241]. Shi-zhen Li (1518-1593), a famous Chinese physician in history and the author of Compendium of Materia Medica, suggested using ficus carica to treat hemorrhoidal disease [267]. In physiological reality, higher expression of VEGF exists in hemorrhoidal tissue [268], and it was found that constipated children had significantly lower intakes of vitamin C [269]. Moreover, ficus carica decreases VEGF level significantly [270] and is an excellent source of ascorbic acid [271]. These indicate that the pathogenesis and treatment strategy of modern medicine are the same as those of TCM.

TCM considers that kidney is connected with bladder. Yuan-fang Chao (550-630) stated that kidney and bladder controls micturition, and deficient Kidney Qi (or NO) causes frequent urination and nocturnal enuresis [260]. In physiological reality, NO synthase plays a functional role for controlling micturition [272], neuronal NO synthase gene polymorphism may be associated with primary nocturnal enuresis in children [273], and Nicorandil, a nitric oxide donor, improves the frequent urination [274]. These are consistent with the statement of TCM.

TCM considers that liver is connected with gallbladder. TCM considers that one of the pathogenesis of gall stone is Liver Qi melancholy, and one of the pathogenesis of cholecystitis is Liver Qi (or GSH) stagnation [275]. In physiological reality, gall stone patients have altered gallbladder functions and their GSH levels are lower than those of gall stone free subjects [276]; in acute cholecystitis patients, the total glutathione in blood is lower while the activity of glutathione metabolism enzymes in red blood cells is inhibited [277]. The pathogenesis is consistent with that of TCM.

Taking hypertension as another example. TCM physicians consider that one of the pathogenesises of hypertension is “Liver Yang is hyperactive” [278]; in physiological reality, chronic administration of EPO induces hypertension [279], and serum HGF concentration in

hypertensive patients is significantly higher than that in normal subjects [280]. TCM considers another pathogenesis of hypertension is “Both Kidney Yin and Liver Yin are deficient” [278]; in physiological reality, hypertension patients had low or undetectable levels of plasma renin activity [281], localized loss of pulmonary artery extracellular SOD augments chronic hypoxic pulmonary hypertension [282], AKR activity is significantly low in spontaneously hypertensive rat medulla [283], and hypertension is associated with downregulation of canonical Wnt signaling pathways [284]. All of these examples indicate that TCM and modern medical science are describing the same thing but using different terminology!

The direct mapping between TCM and signaling molecules enables us to investigate the effect of balance of signaling molecules on human health and understand the closed-loop of pathways of these molecules, that would lead to new therapeutic strategies and insight into the rules governing physiological processes.

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